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De novo cost-utility analysis of oral paliperidone in the treatment of schizoaffective disorder

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ABSTRACT

Objectives: The aim of this analysis is to compare costs and effectiveness of paliperidone ER vs. placebo in the treatment of schizoaffective disorder (SAD) in the Czech Republic based on pooled clinical trial data.
Methods: A de novo micro-simulation model was developed to assess the cost-utility analysis of paliperidone vs. placebo as there is lack of clinical data comparing paliperidone to other interventions. There are no studies primarily evaluating the efficacy of treatment of SAD with other antipsychotics. The model estimated effectiveness and costs of patients with SAD every week during 24-week time horizon. The effectiveness was defined as improvement of a patient's PANSS score where utilities were assigned to each modelled PANSS score. Based on the patient level data a linear mixed-effects model was used to estimate the regression equations of percentage decrease of PANSS score from the baseline. Utilities were computed using a regression function of patients' age, sex and PANSS score, which was adapted from a clinical study of patients with schizophrenia as there are no QoL data on SAD patients. Among relevant costs, reflecting the payer's perspective, costs of pharmacotherapy, concomitant medications and outpatient care were considered.
Results: The average ICER of paliperidone compared to placebo reached 28,935 EUR/QALY. The probability of paliperidone being cost-effective compared to placebo was 99.5%.
Conclusions: Treatment of SAD with paliperidone results in acceptable ICER and high probability of being cost-effective compared to placebo. Thus, it can be considered as a cost-effective treatment of patients with SAD in the Czech Republic.

1. Introduction

Schizoaffective disorder (SAD) is a common, chronic, and disabling mental illness with a high risk of suicidal behaviour. Schizoaffective disorder is characterized by the concurrent manifestation of primary symptoms of schizophrenia (such as delusions, hallucinations, disorganized speech, and disorganized behaviour) and prominent affective symptoms consistent with major depression or mania (Canuso et al., 2010b).

Estimates of the lifetime prevalence of schizoaffective disorder range from 0.2% to 1.1% (Abrams et al., 2008). The incidence of schizoaffective disorder and schizophrenia ranges approximately from 24% to 32% among frequent users of mental health services (Kent, 1995).

The PANSS, or the Positive and Negative Syndrome Scale, is a widely used medical scale for measuring symptom severity of patients with schizophrenia. The PANSS scale contains positive, negative and general psychopathologic components. The total PANSS score is obtained as the sum of scores in the general component and the difference between positive and negative components scores and it varies between 30 and 210 points.

Paliperidone (9-hydroxy-risperidone, R076477) is an atypical antipsychotic agent approved for the treatment of schizophrenia and for the treatment of bipolar disorder and schizoaffective disorder. Paliperidone is a monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5-hydroxytryptamine [5-HT]) type 2A (5HT2A) antagonism of the newer (second-generation) antipsychotic drugs (Canuso et al., 2010a). Paliperidone is available in an oral formulation using

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extended-release (ER) osmotic pump technology (OROS®), referred to as paliperidone ER (INVEGA®).

Paliperidone ER is the only active treatment evaluated within randomised placebo-controlled clinical trials designed primarily for SAD. There are no head-to-head clinical data comparing effectiveness of paliperidone and other antipsychotics in the treatment of SAD. The clinical data for any other antipsychotics in treatment of SAD are very limited. Moreover, there are no general guidelines for SAD treatment. This cost-utility analysis (CUA) is based on two clinical trials, R076477-SCA-3001 (Canuso et al., 2010a) and R076477-SCA-3002 (Canuso et al., 2010b), where placebo was used as the comparator to paliperidone ER.

The primary objective was determination of cost-effectiveness of paliperidone versus placebo as there is no clinical data comparing paliperidone to other interventions.

2. Material and methods

2.1. Data

The model is based on pooled patient-level data of the intent-to-treat (ITT) analysis set of the two phase III clinical trials R076477-SCA-3001 and R076477-SCA-3002 (Canuso et al., 2010a) (Canuso et al., 2010b). The rationale for pooling these studies was to increase the pool of patients for modelling and thus to get more accurate estimates. The pooling was possible as study designs and study populations were very similar. In these phase III studies, the population consisted of adult patients with a Structured Clinical Interview for DSM-IV Disorders (SCID)-confirmed DSM-IV diagnosis of schizoaffective disorder and experiencing an acute exacerbation. Characteristics of the population in the studies are summarized in Table 1. The ITT analysis set consisted of all subjects who were randomly assigned to treatment, received at least 1 dose of study medication and completed baseline and at least 1 post-baseline PANSS assessments. The key observed characteristics of patients used to model the population were age, sex, baseline PANSS score, mean daily dose and information on whether the patient was receiving concomitant medication – antidepressants (AD) and/or mood stabilizers (MS) – or not.

In the study R076477-SCA-3001, 316 subjects were randomized and of these, 310 (98%) received at least 1 dose of study medication and had at least 1 post-baseline PANSS assessment, and thus were included in the ITT analysis set. In the study R076477-SCA-3002, 311 subjects were randomized and of these, 304 (98%) were included in the ITT analysis set. For the pooled data (Canuso et al., 2010c), a total of 627 subjects were randomly assigned to double-blind treatment. Of these, 614 subjects (98%) were included in the pooled ITT analysis set, including 200 patients who were treated with placebo and 414 patients who received paliperidone ER.

The primary efficacy end point in these studies was the change in the PANSS total score from baseline to the Week 6 LOCF (last observation carried forward) end point.

In the ITT analysis of the two phase III studies values of PANSS were measured for Day 4 and Weeks 1, 2, 3, 4, and 6 during the double-blind treatment phase. If any value of measurement was missing, the LOCF approach was applied. Thus, if a patient was withdrawn after Day 15, the values of the PANSS score for Week 3, 4 and 6 equal the value on Day 15.

Paliperidone ER tablets were orally administered once daily across the dose range of 3–12 mg. In the study R076477-SCA-3001, patients were randomized in a 1:1:1 ratio to 1 of 3 groups to receive treatment with paliperidone ER low dose (6 mg/day, with an option to reduce to 3 mg/day, n = 105), paliperidone ER high dose (12 mg/day, with an option to reduce to 9 mg/day, n = 98) or placebo (n = 107). In the study R076477-SCA-3002, patients were randomized in a 2:1 ratio to receive treatment with paliperidone ER in a flexible dose range of 3–12 mg/day (starting dose 6 mg/day, n = 211) or placebo (n = 93).

2.2. Time horizon, discounting and perspective

The observation period of the two phase III studies was only 6 weeks, therefore the data are not sufficient for extrapolation in long term periods as it could be uncertain. Within the sensitivity analysis the time horizon was extended to 52 weeks and a scenario including 12 weeks was considered as well. Discounting was not used as the time horizon does not exceed 1 year. The cost-utility analysis is designed from the perspective of a public healthcare payer. Relevant costs drawing resources only from public insurance funds were included in the model.

2.3. Effectiveness

The clinical effect of treatment considered in the model was the improvement of patients' health state expressed as the decrease of the PANSS score over the examined time period. A linear mixed-effects (LME) model was used to estimate the regression equation of percentage change of post-baseline PANSS score from the baseline for each treatment. LME models expand linear regression models as they enable to describe the variability from the different observational level perspective and also from the perspective of single subjects. Estimated equations determine the percentage change of PANSS score from the baseline on a daily basis. The estimates were computed in the R software (R Core Team, 2004) and the nlme package (Pinheiro et al., 2014). Pooled data were stratified by the treatment arm and regression equations were estimated separately for paliperidone and placebo arm.

From the tested combinations of explanatory variables and forms of regression, the only explanatory variable statistically significant at the 5% level for both treatment arms was the variable ln(t) indicating logarithmic regression (t is time in days). Regression equations including only ln(t) as an explanatory variable (Fig. 1) had

Table 1
Population characteristics.

	Placebo	Paliperidone	Total
ITT (No. of patients)	200 (33%)	414 (67%)	614 (100%)
Concomitant medication – Antidepressants	80 (13%)	131 (21%)	211 (34%)
Concomitant medication – Mood stabilizers	82 (13%)	175 (29%)	257 (42%)
Male	121 (20%)	250 (41%)	371 (60%)
Female	79 (13%)	164 (27%)	243 (40%)
Age			
18–25	29 (5%)	54 (9%)	83 (14%)
26–50	147 (24%)	321 (52%)	468 (76%)
≥51	24 (4%)	39 (6%)	63 (10%)
Mean (SD)	37.2 (10.31)	37.5 (9.66)	37.4 (9.87)